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09/720,933	03/01/2001	Elisabeth Henriette Burger	702-002201	8311

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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,933	BURGER ET AL.	
	Examiner	Art Unit	
	Thomas S Heard	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34-68 are provisionally rejected under the judicial created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of copending Application No. 10/627,314. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of 10/627,314 application encompasses the instant claims. The other claims of 10/627,314 render the instant claims obvious because a bone composition and an amphiphilic antimicrobial agent of a histatin analogue are claimed. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not understood what is meant by domain in this application. Domain is defined by Gracy et al, "DOMO: A New Protein Domain Database," http://www.infobiogen.fr/services/domo/ as "independent and globular folding units within a three-dimensional protein structure." These domains are regions, usually highlighted or illustrated in the primary sequence of the protein, that have a distinct function, fold, that may or may or not be amphiphilic. As claimed, "an amino acid chain which contains a domain of 10 to 25 amino acids, where in the majority of the amino acids of the one half of the domain is positively charged and the other half of the domain is uncharged amino acids" simply describes a ten amino acid sequence whereby the first 5 amino acids of the domain could be arginine and the last five amino acids could be alanine –amphiphilicity is not described by the term domain. A domain of a peptide or protein speaks of a region of the molecule but does not describe the structure and, thus, might be amphiphilic or non-amphiphilic. Additionally, "an amino acid chain which "**contains**" a domain of 10 to 25 amino acids " is open language and is descriptive of untold number of proteins that have a "stretch of amino acids" that have basic residues in the first half of the primary sequence and uncharged residues in the C-terminal half. The size of the peptide/protein is indefinite.

Claim 66 recites the limitation "The method ..as claimed in claim 35" in line 1. There is insufficient antecedent basis for this limitation in the claim. Please note that claim 35 is drawn to a product not a method and, therefore, this phrase lacks antecedent basis. It is suggested that the word "The" within this phrase be replaced by --A-- to overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-41, 50-56, 58-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for synthetic histatin analogues, does not reasonably provide enablement for an amphiphilic/amphipathic α-helix as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Histatin analogues, as taught by Helmerhorst et al, "Synthetic histatin analogues with broad-spectrum antimicrobial activity," 1997, Vol. 326, pages 39-35, are shown to have antimicrobial properties due to their membrane-active, amphiphilic structure. Helmerhorst also points out that amphiphilicity is also a property of protein folding which is not an antimicrobial property, see discussion on pages 43 and

44. Thus Helmerhorst discloses that "helical conformation with lateral amphipathicity" is a key component for antimicrobial activity, but not a guarantee of that property. One skilled in the art would know how to synthesize a peptide in general, but not know how to combine the plurality of amino acids to synthesize all antimicrobial analogues of histatin.

Claims 35-41, 50-56, 58-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the

claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention*.

In the instant case, the claims are drawn to amphiphilic, antimicrobial peptides.

(1) Level of skill and knowledge in the art:

The level of skill to practice the art of the instantly claimed invention is high.

(2) Partial structure:

Derivatives of histatin, specifically those of claims 42-49 and 57.

(3) Physical and/or chemical properties:

Peptides of naturally occurring and non-natural amino acids that are synthesized in such a manner that they may form an amphiphilic, α–helix.

(4) Functional characteristics:

Membrane penetrating peptides that lethally disrupt the lipid bi-layer of bacteria.

(5) Method of making the claimed invention:

Standard peptide synthesis known to one skilled in the peptide art.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims 35-41, 50-56, 58-65 is a broad generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of antimicrobial, amphiphilic peptide. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. While having written description of histatin derivatives and compounds identified in the specification tables and/or examples, the specification is void of any peptides, organic molecules that qualify for the functional characteristics claimed as the biomolecules, and polymers with functional characteristics that qualify.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 35-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamanishi et al, "A Self-Setting TTCP-DCPD Apatite Cement for Release of Vancomycin," Journal of Biomedical Research (applied Biomaterials), Vol. 33, 139-143 (1996) and Helmerhorst et al, "Synthetic Histatin Analogues with Broad-Spectrum Antimicrobial Activity," Biochem J, Vol. 326, 39-45 (1997). Hamanishi et al teaches a "tetracalcium phosphate-dicalcium phosphate dihydrate (TTCP-DCPD) apatite cement" that hardens into a hydroxyapetite phase that is similar to bone and incorporates (includes) Vancomycin for the treatment of osteomelytis. Hamanishi teaches that the TTCP-DCPD cement can accommodate many drugs without denaturation (if a peptide drug), see page 139 and first paragraph, and page 142 and second column. Hamanishi further teaches the method of mixing the cement powder in a liquid medium in combination with Vancomycin and allowing the bone cement mixture to set. *In vivo* data is provide in support of the release of the antibiotic and osteomelytis treatment. Hamanishi does not teach the incorporation of amphiphilic, antimicrobial peptides of histatin analogues disclosed in the instant application.

Helmerhorst et al teaches the amphiphilic histatin analogues of the instant application and their use as an antimicrobial inhibitor. Helmerhorst teaches that these amphiphilic peptides have broad-spectrum range against a variety of fungal and microbial strains and explains that these peptides are good alternatives/supplements and bacteria do not show resistance to these types of antimicrobial compounds.

It would have been obvious to one of ordinary skill in the art to modify the method of treating the above osteomelytis by using the bone cement, as taught by Hamanishi et

al, and incorporate a broader based antimicrobial peptide(s) of histatin analogues as taught by Helmerhorst et al. One of ordinary skill in the art would have been motivated to do so given a recognized benefit of a broader spectrum antimicrobial/antifungal, amphiphilic peptide, and there would have been a reasonable expectation of success given that TTCP-DCPD in combination with Vancomycin has been successfully used to treat osteomelytis, and TTCP-DCPD can incorporate numerous drugs without any deleterious effect on their structure or activity. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-40, 50-56, and 58-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Haque, "Influence of Milk Peptides in Determining the Functionality of Milk Proteins: A Review," Journal of Dairy Science, 1993, Vol. 76, pages 311-320 and evidenced by Meisel, "Biochemical Properties of Regulatory Peptides Derived from Milk Proteins," Biopolymers, 1997, Vol. 43: 119-128 and Kraft Foods

http://www.kraftfoods.com/kf/HealthyLiving/mob/dairy.htm. Milk is rich in calcium (calcium carbonate and calcium phosphate, components of hydroxylapatite that form bone) and is thus milk reads on bone material. Haque discloses that the milk is naturally rich in amphiphilic peptides, for example see abstract on page 311, and Meisel discloses that enzymatic hydrolysis releases numerous amphiphilic peptides of with antimicrobial activity, see pages 123 and 124. The word "contains" is open language and thus, milk proteins meets the limitation of the claim of bone material containing amphiphilic, antimicrobial peptides. Further, "cement" and "cure" is not defined in the specification and can thus read on the sticky scum found after the water has evaporated.

Objections

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. ' 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. " 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Specifically, the sequences in the claims must be identified by SEQ ID NOS:.

Conclusion

No claims allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TSH

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